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Monitoring Neovascularity as an Indicator of Response to Chemotherapy in Osteogenic and Ewing Sarcoma Using Magnetic Resonance Angiography

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Histologic studies on resected specimen have shown that tumor neovascularity is related to prognosis and response to therapy in a variety of human neoplasms. In nine patients with osteogenic or Ewing sarcoma, we evaluated the use of magnetic resonance angiography (MRA) to assess neovascularity non-invasively in vivo and to monitor response to chemotherapy. Seven patients with osteosarcoma and two patients with Ewing sarcoma were studied before and after chemotherapy by MRA (2-D time-of-flight gradient-echo sequence, TR = 50 msec, TE = 9.5 msec, θ = 50°, acquisition time 13 min). MR angiograms were assessed for chemotherapy-induced changes in neovascularity. MRA showed both feeder vessels and neovascularity. Six patients responded to chemotherapy (≥90% histologic tumor necrosis). MRA demonstrated marked reduction in neovascularity in all responders. Three patients did not respond to chemotherapy (<90% histologic tumor necrosis). MRA demonstrated persistent or increased neovascularity in the nonresponders. MRA provides a unique opportunity to study tumoral neovascularity noninvasively in vivo and helps to assess response to chemotherapy in patients with osteogenic or Ewing sarcoma. These general principles may be applicable to other human tumors.

Key words: bone tumor, osteogenic sarcoma, chemotherapy, magnetic resonance imaging, musculoskeletal neoplasm, Ewing sarcoma, magnetic resonance angiography

INTRODUCTION

Prior to the introduction of chemotherapy, the prognosis was poor in osteosarcoma and Ewing sarcoma, and 70–90% of patients died of metastases [1]. Disease-free survival rate is significantly greater in patients who respond to chemotherapy than in nonresponders [2,3]. The efficacy of chemotherapy is usually assessed by histologic analysis of tumor specimens after resection. Response is considered good when >90% of the tumor cells have been devitalized [4].

Clinical signs such as decrease in pain and soft tissue mass are inadequate in determining the efficacy of preoperative chemotherapy and have poor correlation with histologic response [2]. It is difficult to evaluate the response of a tumor to chemotherapy prior to surgical resection and histologic analysis, although such early assessment of therapeutic efficacy would help guide the choice of drug therapy and, ultimately, improve outcome.

Intra-arterial angiography has been employed previously for monitoring response to chemotherapy in patients with osteosarcoma and Ewing sarcoma [5,6]. Intra-arterial angiography is, however, invasive and requires arterial catheterization. Procedural complications such as hematoma and arterial dissection may occur. These drawbacks and the concomitant advances in CT and magnetic resonance imaging (MRI) have markedly reduced the use of intra-arterial angiography in patients with primary bone tumors.

Two-dimensional, time-of-flight magnetic resonance angiography (MRA) may provide information similar to that obtained with intra-arterial angiography with fewer complications and without ionizing radiation. MRA has been used successfully for evaluating peripheral vascular disease [7]. We describe the use of MRA in monitoring

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response to chemotherapy in patients with osteosarcoma and Ewing sarcoma and compare the results obtained with this technique with those obtained by histologic analysis of the resected specimens.

MATERIALS AND METHODS

Seven patients with osteosarcoma and two patients with Ewing sarcoma, with a mean age of 15.7 years, were studied before and after chemotherapy by MRI and MRA. The study had been approved by the Committee on Human Research at our institution, and all patients and/or their legal guardians had signed informed consent. MRI and MRA were generated using a 1.5T GE Signa MR system with a knee coil or surface coils. MRA was performed using a thin-section, 2-D time-of-flight gradient-echo sequence (TR = 50 msec, TE = 9.5 msec, $\theta = 50°$, 2 NEX, matrix 256 × 128, field of view 20 cm). Sixty coronal, 1.5-mm-thick sections were obtained in 13 minutes. Constant velocity flow compensation by gradient moment nulling was used on the section and frequency encoding axes. Individual excitation sections (source images) were postprocessed with a maximum intensity projection (MIP) algorithm.

Conventional axial and coronal MR images were acquired with spin-echo (T1-weighted: TE = 30 msec, TR = 800 msec) and gradient-echo sequences (T2*-weighted: double echo, TE = 14 and 30 msec, TR = 600 msec, $\theta = 30°$) using two excitations, a matrix of 256 × 192 elements, and 5 mm slice thickness without interslice gap. T1-weighted spin-echo images were repeated after i.v. administration of 0.1 mmol/kg body weight gadopentetate-dimeglumine (Magnevist®, Berlex). Prechemotherapy studies were performed at time of diagnosis; postchemotherapy MRI and MRA were obtained 3–5 days prior to limb-salvage surgery in all patients.

Images were interpreted by two radiologists blinded to clinical and histologic information in a joint reading. Tumor neovascularity by MRA was graded low (0–3 neovascular structures/cm^2 tumor), intermediate (4–5 neovascular structures/cm^2 tumor), and high ($\geq$6 neovascular structures/cm^2 tumor). Changes in pre- and postchemotherapy neovascularity were compared and related to histologic findings after surgical resection of the tumor. Histologic response to chemotherapy was graded good when 90% or more of the tumor was necrotic and poor when tumor necrosis was <90%.

RESULTS

MRA showed normal vascular structures, feeder vessels, and tumor neovascularity (Figs. 1, 2). Neovascularity was characterized by an irregular caliber, a distorted course, and abrupt angulations. Prior to chemotherapy, neovascularity was graded high in eight patients (Fig. 1B) and intermediate in one patient (Fig. 2A). By histologic criteria, six patients responded favorably to chemotherapy and three patients were nonresponders. In all six responders, neovascularity decreased markedly and was graded low on follow-up MRA after chemotherapy (Fig. 1). Additionally, feeder vessels were seen to decrease in amount and caliber in responders (Fig. 1). Conventional MRI showed a decrease in tumor size in five and development of nonenhancing central tumor necrosis in all six responders.

In the nonresponders, neovascularity remained high and unchanged in one and increased even further after chemotherapy in two patients (Fig. 2). The number of feeder vessels remained unchanged in two and increased in one nonresponder. Conventional MRI showed an increase in tumor size in all three nonresponders despite chemotherapy.

DISCUSSION

Assessment of the efficacy of chemotherapy is important so that nonresponders can be identified and a more appropriate drug regimen can be chosen. MRI is used frequently for monitoring response to chemotherapy in patients with primary musculoskeletal neoplasm. Criteria on MRI for response to chemotherapy include tumor shrinkage [8], tumor signal intensity change, and development of non-enhancing central tumor necrosis [9]. However, marked overlap has been reported between responders and nonresponders using these parameters [8]. Conventional MRI also does not permit visualization of feeder vessels and tumor neovascularity.

MRA can be appended to an existing MR imaging protocol for bone and soft tissue tumors with little additional time requirement. Findings on MRA are similar to those reported for intraarterial angiography [5]. On intraarterial angiography, responders are characterized by a decrease or disappearance of tumor neovascularity, whereas nonresponders show persistence of neovascularity [5]. Correlation between findings on intraarterial angiography and histologic response is reportedly good [6]. The same appears to be true for MRA in our study; we observed no overlap in MRA findings between responders and nonresponders.

Noninvasiveness and absence of ionizing radiation mean that MRA can be repeated during treatment and follow-up of children with osteosarcoma or Ewing sarcoma without fear of complications. Using additional sequences such as velocity encoded cine MR imaging [7], quantitative information on tumor blood flow may be obtained in addition to morphologic evaluation of neovascularity. In the future, diagnostic accuracy in assessing the efficacy of chemotherapy may advance beyond current standards by combining information on tu-

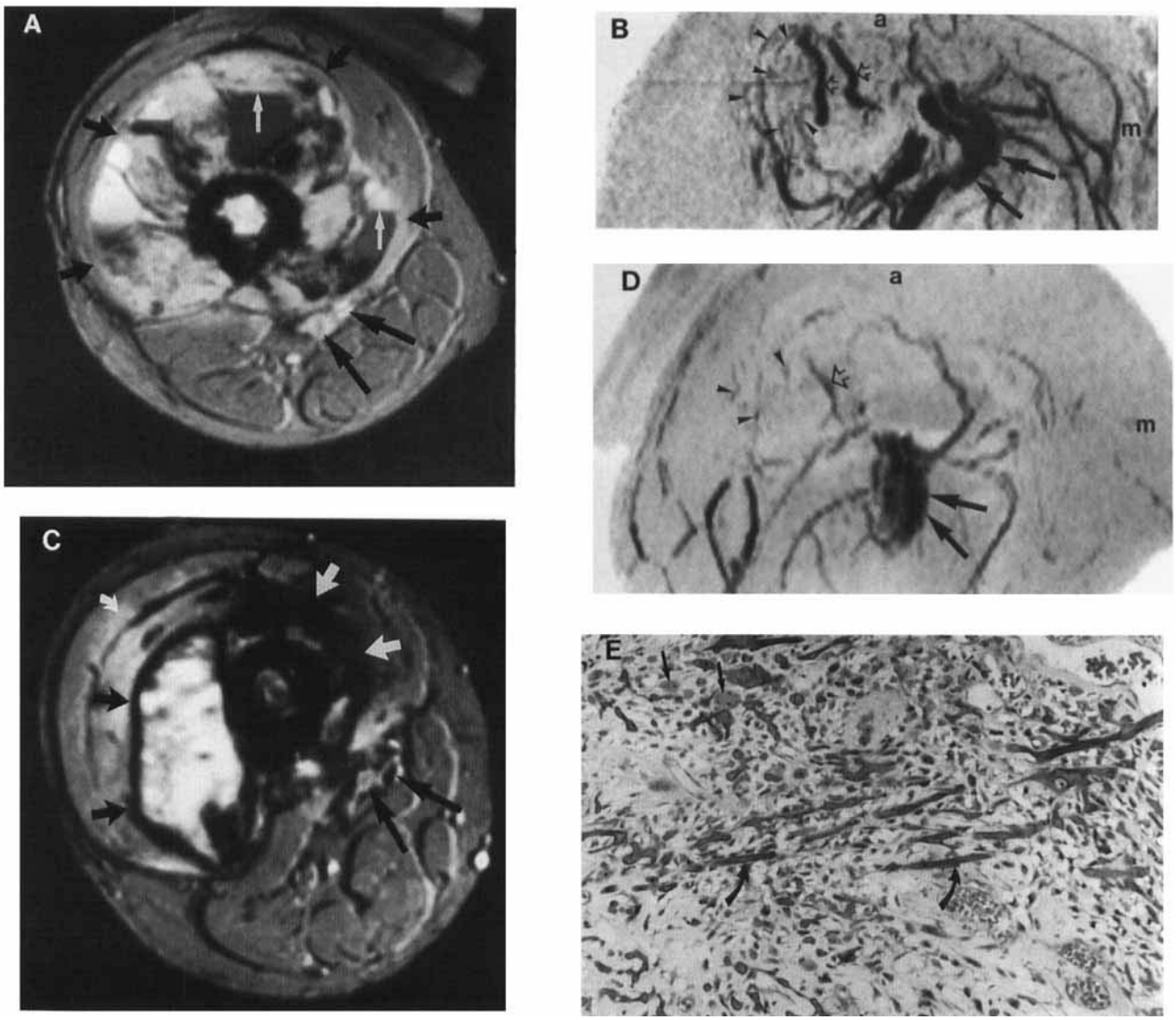

Fig. 1. Osteosarcoma in proximal femur—responder. **A.** T2*-weighted axial gradient-echo MRI (TR = 600 msec, TE = 30 msec, θ = 14°) obtained prior to chemotherapy shows large medial and lateral tumor soft tissue mass (short black arrows). Fluid-fluid levels (white arrows) are present probably reflecting tumor hemorrhage. Femoral artery and vein are seen posteriorly with high signal intensity (long black arrows). **B.** Pre-chemotherapy MRA (a: anterior, m: medial). Axial MIP shows femoral artery and vein (solid arrows). High neovascularity is seen in area of tumor (arrowheads). Two large feeder vessels are shown in periphery (open arrows). **C.** T2*-weighted gradient-echo MRI (TR = 600msec, TE = 30 msec, θ = 14°) obtained after chemotherapy immediately prior to surgical resection. Anteromedial soft tissue mass (white straight arrows) has decreased in size suggesting good response. Lateral soft tissue mass shows rim with low signal intensity (short black arrows) reflecting elevated periosteum and scar surrounding an area of uniform high signal intensity, which corresponded histologically to liquefied tumor necrosis. Vastus lateralis muscle shows diffuse edema with high signal intensity (curved arrow). Femoral artery and vein are seen posteromedially (long black arrows). **D.** Postchemotherapy MRA (MIP, axial view, a: anterior, m: medial). Femoral artery and vein are shown in center (solid arrows). Neovascularity has markedly decreased (arrowheads) and is low in density. Previously noted feeder vessels have decreased in number and caliber; only one thin feeding vessel is present medially (open arrow). **E.** Photomicrograph (H + E, 40× magnification) from surgical specimen confirms good response to chemotherapy (≥90% tumor necrosis). Granulation tissue predominates this field. Some tumor osteoid (curved arrows) and only few residual tumor cells are present (straight arrows). Most of the tumor was entirely necrotic.

mor size and morphology derived from conventional pre- and postcontrast MRI with information on tumoral neovascularity seen on MRA. Since tumor shrinkage is related to vascular supply of the tumor, changes in neovascularity are likely to occur before a decrease in tumor volume. MRA may thus help to assess therapeutic efficacy early in the course of chemotherapy.

Furthermore, MRA offers a unique opportunity to study tumor neovascularity in vivo. This concept can be expanded to other human neoplasms such as invasive

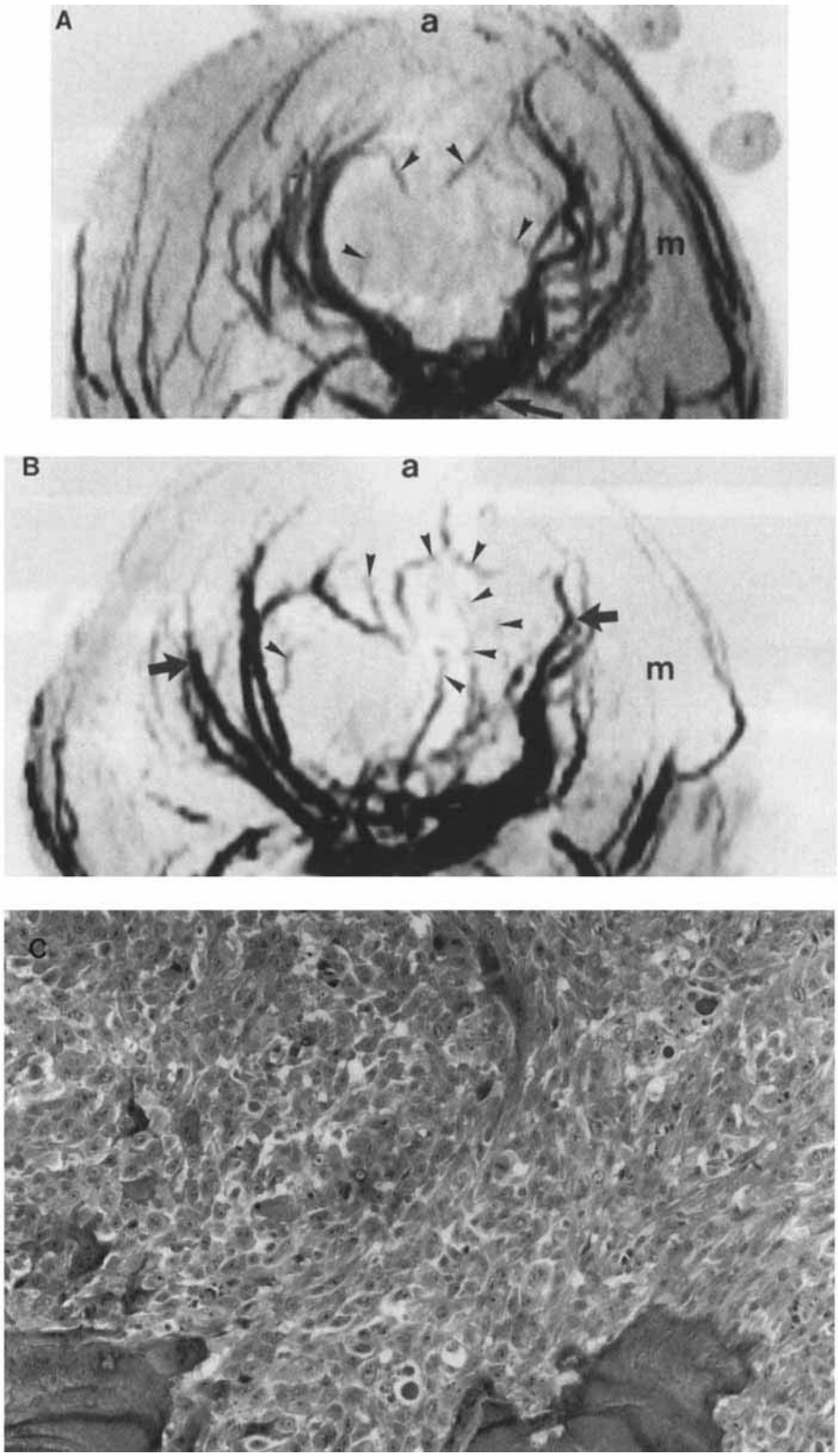

Fig. 2. Osteosarcoma in proximal femur—nonresponder. **A.** Pre-chemotherapy MRA (a: anterior, m: medial). Axial MIP shows neovascularity with intermediate density (arrowheads). Femoral artery and vein are seen posteriorly (arrow). **B.** Postchemotherapy MRA (MIP, axial view, a: anterior, m: medial). The tumor has expanded and feeder vessels are laterally and medially displaced (arrows). High density neovascularity that has increased when compared to the pre-chemotherapy study (in A) is seen coursing toward the center of the tumor (arrowheads). These findings are consistent with nonresponse to chemotherapy. **C.** Photomicrograph (H + E, 40× magnification) obtained after chemotherapy confirms nonresponse. Large areas of viable tumor were identified throughout the resected specimen.

breast carcinoma to assess tumoral neovascular density, which appears to correlate with tumor aggressiveness and presence or absence of metastases [10]. MRA may thus potentially be helpful to determine the prognosis of other neoplasms noninvasively in vivo.

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